Thrombectomy vs. medical management for large vessel occlusion strokes with minimal symptoms

IASON-STEFANOS ANAGNOSTOPOULOS[1], VASILIKI EPAMEINONDAS GEORGAKOPOULOU[2], ILIAS TRAKAS[2], PETROS PAPALEXIS[3,4], NIKOLAOS TRAKAS[5], DEMETRIOS A. SPANDIDOS[6] and GEORGE FOTAKOPOULOS[7]

[1]Medical School, University of Ioannina, 45500 Ioannina; [2]Department of Infectious Diseases and COVID-19 Unit, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens; [3]Unit of Endocrinology, First Department of Internal Medicine, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, 11527 Athens; [4]Department of Biomedical Sciences, University of West Attica, 12243 Athens; [5]Department of Biochemistry, Sismanogleio Hospital, 15126 Athens; [6]Laboratory of Clinical Virology, School of Medicine, University of Crete, 71003 Heraklion; [7]Department of Neurosurgery, General University Hospital of Larisa, 41221 Larisa, Greece

Received March 16, 2023; Accepted June 9, 2023

DOI: 10.3892/etm.2023.12076

Abstract. Patients with acute ischemic stroke (AIS) presenting mild symptoms with a low National Institutes of Health Stroke Scale (NIHSS) score ≤8 and also found to have an intracranial large vessel occlusion (LVO) undergo endovascular thrombolysis (ET) or medical management alone. The current study aimed to evaluate the safety and effectiveness of medical management vs. ET therapy among patients with mild AIS symptoms (NIHSS score ≤8) accompanied by LVO. The present meta-analysis included articles involving mild AIS, LVO, thrombectomy/ET and medical management alone published in full-text form (from 1980 to 2022). Collected variables included: First author name, covered study period, publication year, the total number of patients and age, number of males, presence of diabetes mellitus, hypertension, atrial fibrillation, prior ischemic stroke, location, NIHSS of admission, modified Rankin scale, bleeding, morbidity and mortality. After the initial search and applying all exclusion and inclusion criteria, eight articles were left in the final article pool. The total number of patients who underwent ET was 569, compared with 1097 with medical management for LVO strokes with minimal symptoms. The findings of the present meta-analysis study point out that ET management may be associated with a high risk of bleeding and mortality in patients with LVO presenting with mild symptoms (NIHSS score ≤8).

Correspondence to: Dr George Fotakopoulos, Department of Neurosurgery, General University Hospital of Larisa, Mezourlo 1, 41221 Larisa, Greece
E-mail: gfotakop@yahoo.gr

Key words: thrombectomy, thrombolysis, stroke, bleeding, medical treatment

Introduction

Acute ischemic stroke (AIS) is one of the main reasons for death and disability, particularly in an aging society (1). In 61% of stroke patients, administering intravenous thrombolysis with different agents [medical management; urokinase (2.7%), streptokinase (36.8%) and alteplase, recombinant tissue plasminogen activator] within 3-4.5 h of symptom onset has a favorable outcome (2,3). Furthermore, previous studies suggested that medical management is safe and may benefit patients presenting mild AIS symptoms with a low National Institutes of Health Stroke Scale (NIHSS) score (NIHSS score ≤8) and who are also found to have an intracranial large vessel occlusion (LVO) (4-6).

Endovascular thrombolysis (ET), focusing on relieving vessel occlusion in stroke, has been developed as an alternative for medical management or as an adjunct in administration over the past few years (7,8). However, there is limited knowledge about the role of ET in patients with mild symptoms caused by LVO (9). Nonetheless, some studies also proposed that ET may be favorable in patients with severe symptoms (10).

Patients with mild AIS symptoms with an NIHSS score ≤8 also have an intracranial LVO presentation, requiring remarkably complex therapeutic management (11). Unfortunately, LVO in those patients is associated with poor outcomes; they present with mild deficits (12) and because of weak collateral conditions, they can worsen rapidly or progressively (13). Thus, the need for any acute management is often debated since these patients 'only' have mild defects and any therapy has related risks (11).

Given these conflicting observational reports and the lack of randomized data, the present study aimed to evaluate the safety and effectiveness of medical management vs. ET therapy among patients with mild AIS symptoms (NIHSS score ≤8) accompanied by LVO.

Materials and methods

Search strategy. The study searched the comparative articles involving mild AIS and LVO, thrombectomy, and medical management through electronic databases, including the Cochrane Library, Medline (1980-2022.12), PubMed (1980-2022.12), and EMBASE (1980-2022.12). Preferred reporting items for systematic reviews and meta-analyses were applied for establishing protocol and manuscript design (14). The keywords 'mild acute ischemic stroke', 'large vessel occlusion' and 'thrombectomy/endovascular thrombolysis and medical management', which are present in the MeSH list, were used for database search.

Selection of studies. Two of the reviewers (GF and VEG) independently extracted data from the included articles, following the guidelines of the epidemiology of meta-analysis. The following basic information was captured: Main authors; year of publication; total case number in the thrombectomy and medical management groups; study type; outcome indicator; diabetes; hypertension; atrial fibrillation; location; prior ischemic stroke; NIHSS of admission. The extracted data were input into a table designed and standardized according to the Cochrane Handbook. Fig. 1 depicts the flow of the study selection process. In case of disagreement on the information to be retained, another author with authority (this authority was decided upon by all authors prior to commencing the research) had the final say.

Inclusion and exclusion criteria. If an article satisfied the following PICOS criteria, it was considered for inclusion in the present meta-analysis: i) Population limited to patients with mild acute ischemic stroke (NIHSS score ≤8) and LVO on CT angiography [middle cerebral artery M1/M2, intracranial carotid artery (ICA) or vertebrobasilar occlusion]; ii) intervention limited to ET or medical management; iii) studies comparing the outcomes between ET and medical management; iv) one of the primary outcomes, such as morbidity and mortality, was involved. To avoid publication bias, the final aim was to collect a homogenous pool of manuscripts, including articles that compare only two intervention modalities, i.e. ET and medical management. Table I contains detailed data on these articles.

All prospective and retrospective studies that evaluated at least one of the two modalities were included, whereas editorials, reviews, case reports and articles focusing on the pediatric population, unrelated outcomes, co-morbidities, experimental techniques, or one of the two modalities from that article pool, were excluded. In addition, in the case of studies with mixed or unclear results, the corresponding information was removed or was placed into groups accordingly, although without affecting the ratio.

Outcomes' definition. The primary outcomes involved in the present study included mortality and post-intervention morbidity (Karnofsky Performance Score-KPS <80). In addition, to find out the association between ET and medical management, the present collected outcome measurements (secondary outcomes) such as the rates of modified Rankin scale (mRS) scores 0-2 (indicating a good outcome) at discharge and long-term follow-up (3 months for the interventional cohort and bleeding after the intervention). The outcomes reported in the included articles were assessed at least three months after the ET or medical management for large vessel occlusion strokes with minimal symptoms. Additionally, a quality assessment tool was used to decrease the risk of bias in our poor articles (Newcastle-Ottawa Scale; Table II) (15).

Evaluation of the risk of bias. The Cochrane Collaboration tool was used by two reviewers (GF and VEG) to assess the risk of bias in each study (16). The evaluation included random sequence generation, allocation concealment, blinding of participants and assessors, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases (such us criteria of 'unclear risk' of bias; this was in the case of insufficient available information to assess whether an important risk of bias exists or insufficient evidence that an identified problem will introduce bias. The assessment results were classified into low, high and unclear risk levels. The third reviewer arbitrated any disagreements.

Data synthesis and assessment of heterogeneity. All analyses were carried out using Review Manager Software v5.4 (RevMan; https://training.cochrane.org/online-learning/core-software/revman). Heterogeneity across trials was identified using I^2 statistics; considering I^2 >50% as high heterogeneity, a meta-analysis was conducted using a random-effect model according to the Cochrane Handbook for Systematic Reviews of Interventions (v5.1.0) (17). Otherwise, a meta-analysis using the fixed-effect model was performed. The continuous outcomes were expressed as a weighted mean difference with 95% confidence intervals (CIs). For discontinuous variables, odds ratios (OR) with 95% CIs were applied for the assessment. To test the sensitivity, the 'leave out one' model was used by removing one study at a time. P<0.05 was considered to indicate a statistically significant difference.

Results

Articles meeting criteria. A total of eight articles met the eligibility criteria (18-25). The total number of patients was 569 who underwent ET and 1097 with medical management for LVO strokes with minimal symptoms. The study sample was based on eight studies (Table II). Among these, five were retrospective and three were prospective observational studies.

Epidemiological and clinical features. The mean age of the patients was 70.46 years (range, 53-72 years; 64.06 and 76.93 years for the ET and the medical management sample, respectively). The male-to-female ratio was 1:1.7. Diabetes was diagnosed in 325/1666 (19.5%) of patients (123/569 and 202/1097 in the ET and the medical management group, respectively), hypertension in 1186/1666 (71.1%) of patients (405/569 and 781/1097 in the ET and medical management groups, respectively), and atrial fibrillation in 378/1666 (22.6%) of patients (141/569 and 237/1097 in the ET and medical management groups, respectively) (Table I).

Diabetes mellitus. Information regarding diabetes mellitus was available in eight articles (18-25) and demonstrated no statistical result (OR 1.07, CI 95% 0.58-1.40; P=0.61) with no

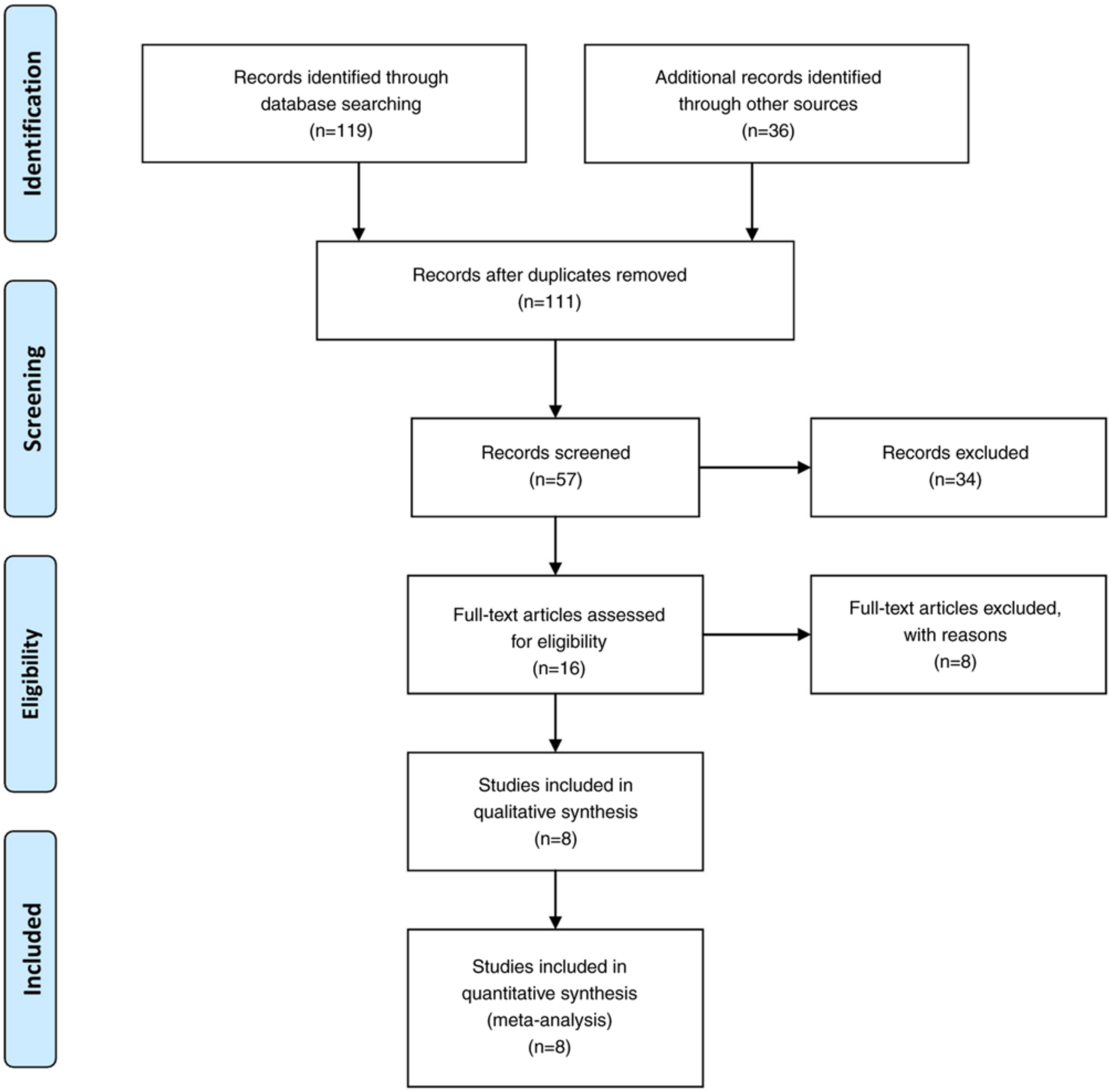

Figure 1. Flow chart.

heterogeneity (P=0.56 and I^2=0%) (Fig. S1). Diabetes mellitus was found in 325 of the 1666 (19.5%) patients in the total group. In the ET group, diabetes mellitus was diagnosed in 123 of 569 (21.6%) patients, compared with 202 of 1097 (18.4%) in the medical management group. Looking at the funnel plot of the same parameter, no publication bias was found.

Hypertension. As regards hypertension, information was available in eight articles (18-25) and demonstrated no statistical result (OR 1.87, CI 95% 0.68-1.10; P=0.23) with no heterogeneity (P=0.83 and I2=0%) (Fig. S2). Hypertension was found in 1186 of 1666 (71.1%) patients in the total group. In the ET group, hypertension was diagnosed in 405 of 569 (71.1%) patients, compared with 781 of 1097 (71.1%) in the medical management group. Looking at the funnel plot of the same parameter, no publication bias was found.

Atrial fibrillation. Atrial fibrillation data were available in eight articles (18-25). Atrial fibrillation was reported for 378 of the 1666 (22.6%) patients in the total group and 141 of the 569 (28.2%) patients in the ET group. The statistical analysis demonstrated no statistically significant difference (OR 1.27, CI 95% 0.85-1.91; P=0.24), but indicated heterogeneity (P=0.07 and I^2=48%) (Fig. 2A). By testing sensitivity (Table III), after removing the article by 'Kastrup *et al*, 2018' (23), a statistically significant difference result was found (OR 1.61, CI 95% 1.18-2.21; P<0.05), with no heterogeneity (P=0.52 and I^2=0%) (Fig. 2B). The total sample size for this combination was 247 (18.1%) out of 1361, of which 84 (19.8%) out of 424 were from the ET group and 163 (17.3%) out of 937 were from the medical management group. Looking at the funnel plot of the same parameter, it was found that the study results without the Karstup *et al*,

Table I. Design and baseline characteristics of the included trials.

	Sample size, n		Mean age (years)		No. of males		Diabetes		Hypertension		Atrial fibrillation		
First author/s, year	Throm	Medic	Throm	Medic	Throm	Medic	Throm	Medic	Throm	Medic	Throm	Medic	(Refs.)
Urra *et al*, 2014	34	44	64	71	24	26	6	6	21	29	9	14	(18)
Haussen *et al*, 2016	10	22	60	68.2	5	15	2	4	6	13	3	8	(19)
Haussen *et al*, 2017	30	88	63.5	73	15	41	9	10	21	63	10	16	(20)
Nagel *et al*, 2018	80	220	65.3	69.5	44	117	13	36	56	159	35	62	(21)
Sarraj *et al*, 2018	124	90	65.8	65.4	72	51	36	27	87	72	NR	NR	(22)
Kastrup *et al*, 2018	145	160	71	72	65	67	32	35	122	129	57	74	(23)
Wang *et al*, 2020	23	24	53.9	64.4	17	17	4	6	17	17	2	2	(24)
Xue *et al*, 2022	123	449	69	68	82	307	21	78	75	299	25	61	(25)

			Location										
	Prior to ischemic stroke		ICA		M1		M2		Vertebrobasilar		NIHSS of admission		
First author/s, year	Throm	Medic	Throm	Medic	Throm	Medic	Throm	Medic	Throm	Medic	Throm	Medic	(Refs.)
Urra et al, 2014	5	2	0	1	13	13	7	16	12	12	4	3	(18)
Haussen *et al*, 2016	2	7	0	3	6	10	1	5	2	3	4	2	(19)
Haussen *et al*, 2017	NR	NR	2	17	11	17	9	17	7	11	4	3	(20)
Nagel *et al*, 2018	NR	NR	10	26	33	48	23	108	6	15	4	3	(21)
Sarraj *et al*, 2018	22	12	21	12	68	21	33	44	0	0	4	3	(22)
Kastrup *et al*, 2018	NR	NR	32	19	62	76	51	65	0	0	8	7	(23)
Wang *et al*, 2020	4	9	6	8	10	5	2	2	5	9	3	3	(24)
Xue *et al*, 2022	19	77	34	110	59	213	20	83	12	12	3	3	(25)

	mRS 0-2 after 3 months		Bleeding		Morbidity		Mortality		
First author/s, year	Throm	Medic	Throm	Medic	Throm	Medic	Throm	Medic	(Refs.)
Urra *et al*, 2014	1	1	4	0	14	14	4	2	(18)
Haussen *et al*, 2016	10	17	0	0	1	5	0	3	(19)
Haussen *et al*, 2017	29	64	2	0	NR	NR	NR	NR	(20)
Nagel *et al*, 2018	68	154	4	3	8	36	3	20	(21)

Table I. Continued.

First author/s, year	mRS 0-2 after 3 months		Bleeding		Morbidity		Mortality		(Refs.)
	Throm	Medic	Throm	Medic	Throm	Medic	Throm	Medic	
Sarraj *et al*, 2018	78	61	17	9	35	28	11	1	(22)
Kastrup *et al*, 2018	86	89	NR	NR	19	22	NR	NR	(23)
Wang *et al*, 2020	16	18	2	0	12	5	1	1	(24)
Xue *et al*, 2022	84	331	10	9	NR	NR	11	24	(25)

M, middle cerebral artery; Throm, thrombectomy; medic, medical management; mRS, modified Rankin scale; NR, not reported.

2018 article (23) displayed an improved dispersion with no publication bias (Fig. 2C and D).

Prior ischemic stroke. As regards the prior ischemic stroke, the total number of patients was 159 (9.5%) out of 1666 patients, of which 52 out of 569 (9.1%) were from the ET group and 107 out of 1097 (9.7%) were from the medical management group. The statistical analysis demonstrated no significant difference (OR 0.97, CI 95% 0.56-1.70; P=0.93) but indicated heterogeneity (P=0.21 and I^2=32%) (Fig. S3A). By testing the sensitivity (Table III), low heterogeneity (P=0.32 or and I^2=14%) was achieved only after removing the articles by 'Urra *et al*, 2014' (18) or 'Wang *et al*, 2020' (24), as the combination with the removed article by 'Urra *et al*, 2014' (18) was of higher quality because the total sample was 152 compared with 146 in the combination without the article by 'Wang *et al*, 2020' (24) (Table III). However, it was found again no statistically significant difference (OR 0.90, CI 95% 0.60-1.36; P=0.63) (Fig. S3B). Looking at the funnel plot of the same parameter, it was found that the study results without the 'Urra *et al*, 2014' (18) article displayed an improved dispersion with low publication bias (Fig. S3C and D).

MRS 0-2 after 3 months. As regards the mRS 0-2 after 3 months, the total number of patients was 1,107 (66.4%) out of 1,666 patients in the total group, of which 372 (65.3%) out of 569 were from the ET group and 735 (67.0%) out of 1097 patients were from the medical management group. The statistical analysis demonstrated no significant difference (OR 1.23, CI 95% 0.79-1.93; P=0.37) but indicated some heterogeneity (P=0.03 and I^2=55%) (Fig. 3A). By testing the sensitivity (Table IV), low heterogeneity (P=0.16 and I^2=35%) was achieved only after removing the article by 'Nagel *et al*, 2018' (21) but it was found again no statistically significant difference (OR 1.01, CI 95% 0.68-1.50; P=0.96) (Fig. 3B). Looking at the funnel plot of the same parameter, it was found that the study results without the 'Nagel S *et al*, 2018' (21) article displayed an improved dispersion with low publication bias (Fig. 3C and D).

Bleeding. Information regarding bleeding was available in seven out of eight articles (18-22,24,25) and demonstrated a statistical result (OR 3.13, CI 95% 1.65-5.95; P<0.05) with no heterogeneity (P=0.33 and I^2=14%) (Fig. 4). Bleeding was found in 60 out of 1666 (3.6%) patients in the total group. In the ET group, bleeding was diagnosed in 39 out of 129 (30.2%) patients, compared with 21 out of 1097 (1.9%) in the medical management group. Looking at the funnel plot of the same parameter, it was found a very low publication bias.

Morbidity. Morbidity data were available in six of the eight articles (18,20-22,24,25): A total of 199 (20.3%) from 976 included patients; and poor KPS in 89 (21.3%) of 416 patients from the ET group. The statistical analysis demonstrated no significant difference (OR 1.02, CI 95% 0.64-1.63; P=0.94) and indicated heterogeneity (P=0.14 and I^2=39%) (Fig. 5A). By testing the sensitivity (Table IV), no heterogeneity (P=0.57 and I^2=0%) was achieved only after removing the article by 'Wang *et al*, 2020' (24) but again without a statistically significant difference (OR 0.87, CI 95% 0.61-1.24; P=0.45) (Fig. 5B).

Table II. NOS quality assessment of final article pool.

		NOS				
First author/s, year	Study design	Selection	Comparability	Exposure	Total scores	(Refs.)
Urra *et al*, 2014	Prosp	3	3	3	9	(18)
Haussen *et al*, 2016	Prosp	3	3	3	9	(19)
Haussen *et al*, 2017	Retro	3	2	2	7	(20)
Nagel *et al*, 2018	Prosp	3	3	3	9	(21)
Sarraj *et al*, 2018	Retro	3	2	2	7	(22)
Kastrup *et al*, 2018	Retro	3	2	2	7	(23)
Wang *et al*, 2020	Retro	3	2	2	7	(24)
Xue *et al*, 2022	Retro	3	2	2	7	(25)

Retro, retrospective; Prosp, prospective; NOS, Newcastle-Ottawa Scale.

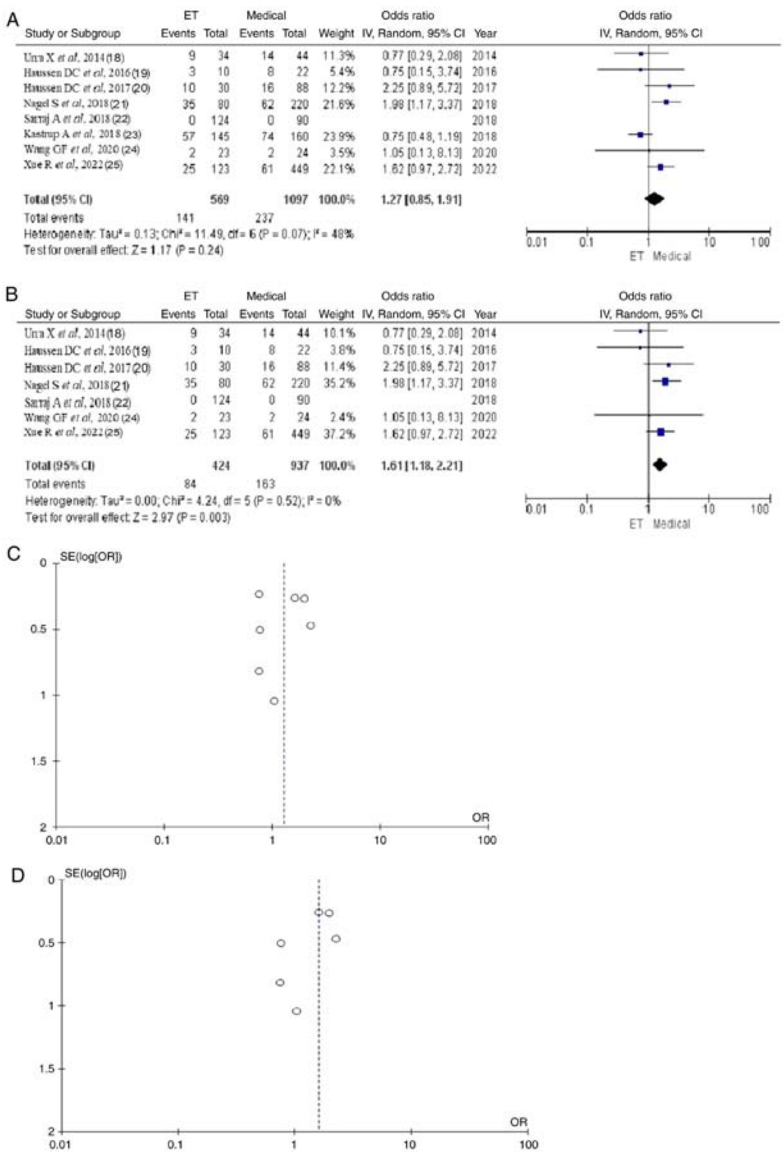

Figure 2. Atrial fibrillation ORs. (A) Forest plot of atrial fibrillation ORs demonstrated no statistically significant difference between the groups (total OR 1.27, CI 95% 0.85-1.91; P=0.24). (B) Forest plot of atrial fibrillation ORs obtained by excluding the 'Kastrup *et al*, 2018' (23) article demonstrated a statistically significant difference between the groups, (total OR 1.61, CI 95% 1.18-2.21; P<0.05). (C) Funnel plot of the atrial fibrillation between groups, with 'Kastrup A *et al* 2018' (23) article and with heterogeneity (P=0.07 and I^2=48 %). (D) Funnel plot of the atrial fibrillation between groups, without 'Kastrup A *et al*, 2018' (23) article and without heterogeneity (P=0.52 and I^2=0%). ET, endovascular thrombolysis; medical, medical management; OR, odds ratio.

Table III. Meta-analysis of clinical parameters.

			Groups		Overall effect			Heterogeneity		
Parameters	Excluded trials	Trials, n	Throm	Medic	Effect estimate	CI 95%	P-value	I^2 (%)	P-value	(Refs.)
Atrial fibrillation	None	8	141	237	1.27	0.85-1.91	0.24	48	0.07	(18-25)
	Urra *et al*, 2014	7	132	223	1.36	0.87-2.12	0.18	52	0.06	(18)
	Haussen *et al*, 2016	7	138	229	1.31	0.85-2.03	0.22	55	0.05	(19)
	Haussen *et al*, 2017	7	131	221	1.18	0.76-1.82	0.46	49	0.08	(20)
	Nagel *et al*, 2018	7	106	175	1.13	0.73-1.73	0.58	36	0.17	(21)
	Sarraj *et al*, 2018	7	141	237	1.27	0.85-1.91	0.24	48	0.07	(22)
	Kastrup *et al*, 2018	7	84	163	1.61	1.18-2.21	<0.05	0	0.52	(23)
	Wang *et al*, 2020	7	139	235	1.28	0.83-1.98	0.26	56	0.04	(24)
	Xue *et al*, 2022	7	116	176	1.19	0.72-1.97	0.50	51	0.07	(25)
Prior to ischemic stroke	None	8	52	107	0.97	0.56-1.70	0.93	32	0.21	(18-25)
	Urra *et al*, 2014	7	47	105	0.90	0.60-1.36	0.63	14	0.32	(18)
	Haussen *et al*, 2016	7	50	100	1.03	0.55-1.96	0.92	45	0.14	(19)
	Haussen *et al*, 2017	7	52	107	0.97	0.56-1.70	0.93	32	0.21	(20)
	Nagel *et al*, 2018	7	52	107	0.97	0.56-1.70	0.93	32	0.21	(21)
	Sarraj *et al*, 2018	7	30	95	0.84	0.39-1.78	0.65	36	0.20	(22)
	Kastrup *et al*, 2018	7	52	107	0.97	0.56-1.70	0.93	32	0.21	(23)
	Wang *et al*, 2020	7	48	98	1.10	0.68-1.80	0.69	14	0.32	(24)
	Xue *et al*, 2022	7	33	30	1.01	0.41-2.49	0.99	46	0.13	(25)
Diabetes mellitus	None	8	123	202	1.07	0.58-1.40	0.61	0	0.56	(18-25)
Hypertension	None	8	405	781	0.87	0.68-1.10	0.23	0	0.83	(18-25)

Throm, thrombectomy; medic, medical management; mRS, modified Rankin Scale.

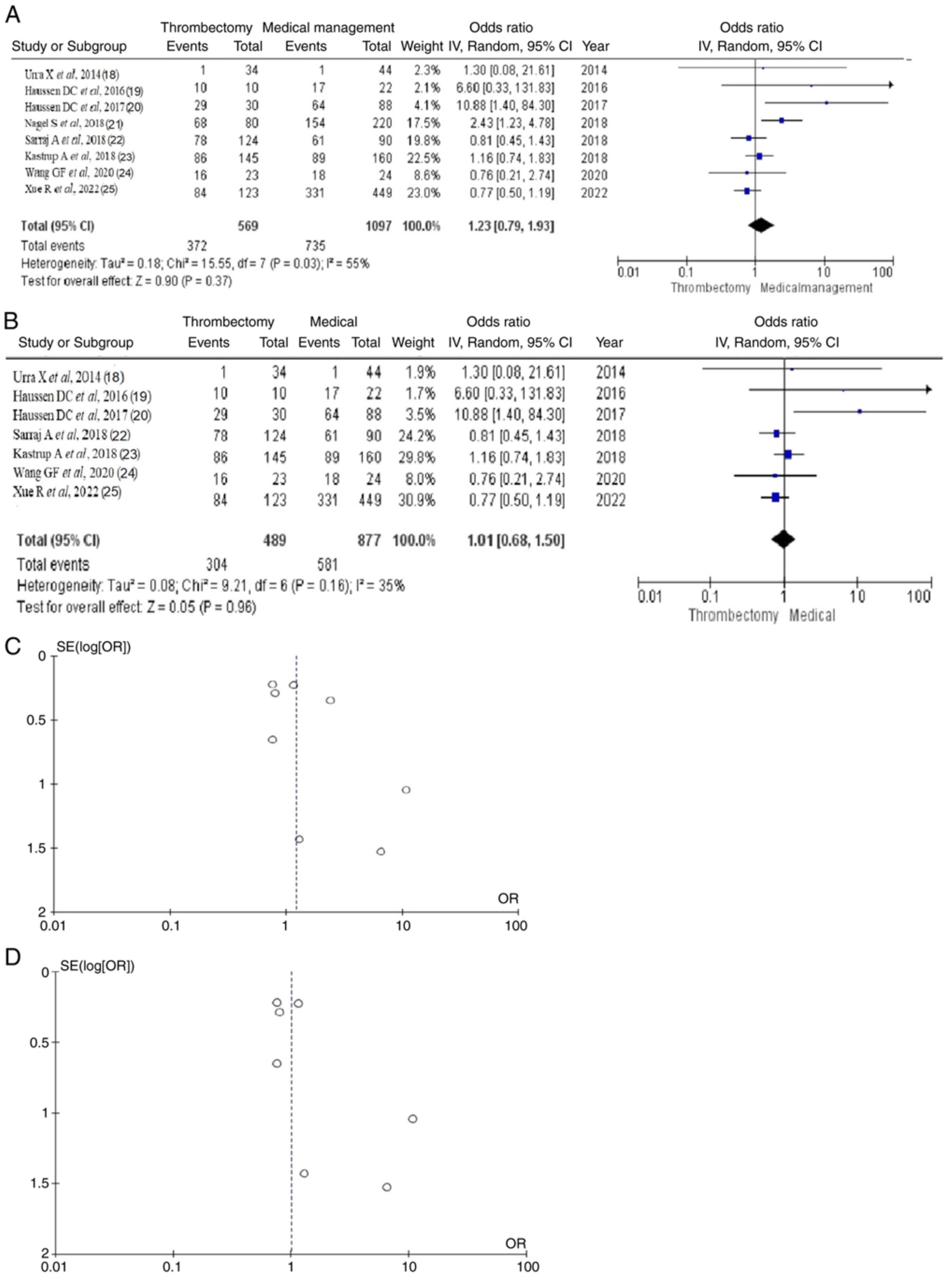

Figure 3. MRS 0-2 ORs after 3 months. (A) Forest plot of mRS 0-2 ORs after 3 months demonstrated no statistically significant difference between the groups (total OR 1.23, CI 95% 0.79-1.93; P=0.37). (B) Forest plot of mRS 0-2 ORs after 3 months obtained by excluding the 'Nagel *et al*, 2018' (21) article demonstrated again no statistically significant difference between groups (total OR 1.01, CI 95% 0.68-1.50; P=0.96). (C) Funnel plot of the mRS 0-2 ORs after 3 months between the groups, including the 'Nagel *et al*, 2018' (21) article and with heterogeneity (P=0.03 and I^2=55%). (D) Funnel plot of the mRS 0-2 OR after 3 months between groups, without 'Nagel *et al*, 2018' (21) article and with low heterogeneity (P=0.16 and I^2=35%). MRS, modified Rankin scale; OR, odds ratio.

Table IV. Meta-analysis of clinical outcomes.

Outcomes	Excluded trials	Trials, n	Groups		Overall effect			Heterogeneity		(Refs.)
			Throm	Medic	Effect estimate	CI 95%	P-value	I^2 (%)	P-value	
mRS 0-2	None	8	372	735	1.23	0.79-1.93	0.37	55	0.03	(18-25)
	Urra *et al*, 2014	7	371	734	1.24	0.77-1.99	0.37	61	0.02	(18)
	Haussen *et al*, 2016	7	362	718	1.18	0.76-1.85	0.46	58	0.03	(19)
	Haussen *et al*, 2017	7	343	671	1.10	0.75-1.61	0.63	43	0.10	(20)
	Nagel *et al*, 2018	7	304	581	1.01	0.68-1.50	0.96	35	0.16	(21)
	Sarraj *et al*, 2018	7	294	674	1.40	0.81-2.42	0.23	58	0.03	(22)
	Kastrup *et al*, 2018	7	286	646	1.32	0.72-2.42	0.36	61	0.02	(23)
	Wang *et al*, 2020	7	356	717	1.31	0.80-2.13	0.29	61	0.02	(24)
	Xue *et al*, 2022	7	288	404	1.43	0.84-2.43	0.19	50	0.06	(25)
Bleeding	None	7	39	21	3.13	1.65-5.95	<0.05	14	0.33	
Mortality	None	6	30	51	1.37	0.55-3.41	0.50	45	0.10	(18,19,21-25)
	Urra *et al*, 2014	5	26	49	1.19	0.40-3.52	0.75	53	0.07	(18)
	Haussen *et al*, 2016	5	30	48	1.56	0.60-4.05	0.36	50	0.09	(19)
	Sarraj *et al*, 2018	5	19	50	1.07	0.46-2.48	0.87	33	0.20	(20)
	Nagel *et al*, 2018	5	27	31	1.94	1.02-3.69	0.04	2	0.40	(21)
	Wang *et al*, 2020	5	29	50	1.41	0.50-3.97	0.51	56	0.06	(22)
	Xue *et al*, 2022	5	19	27	1.27	0.34-4.75	0.73	53	0.08	(23)
Morbidity	None	6	89	110	1.02	0.64-1.63	0.94	39	0.14	(18,19,21-24)
	Urra *et al*, 2014	5	75	96	0.95	0.55-1.64	0.85	45	0.12	(18)
	Haussen *et al*, 2016	5	88	105	1.07	0.65-1.75	0.80	47	0.11	(19)
	Sarraj *et al*, 2018	5	70	88	1.07	0.56-2.01	0.84	51	0.08	(22)
	Kastrup *et al*, 2018	5	81	74	1.16	0.70-1.94	0.56	35	0.19	(23)
	Nagel *et al*, 2018	5	54	82	1.10	0.58-1.09	0.78	50	0.09	(21)
	Wang *et al*, 2020	5	77	105	0.87	0.61-1.24	0.45	0	0.57	(24)

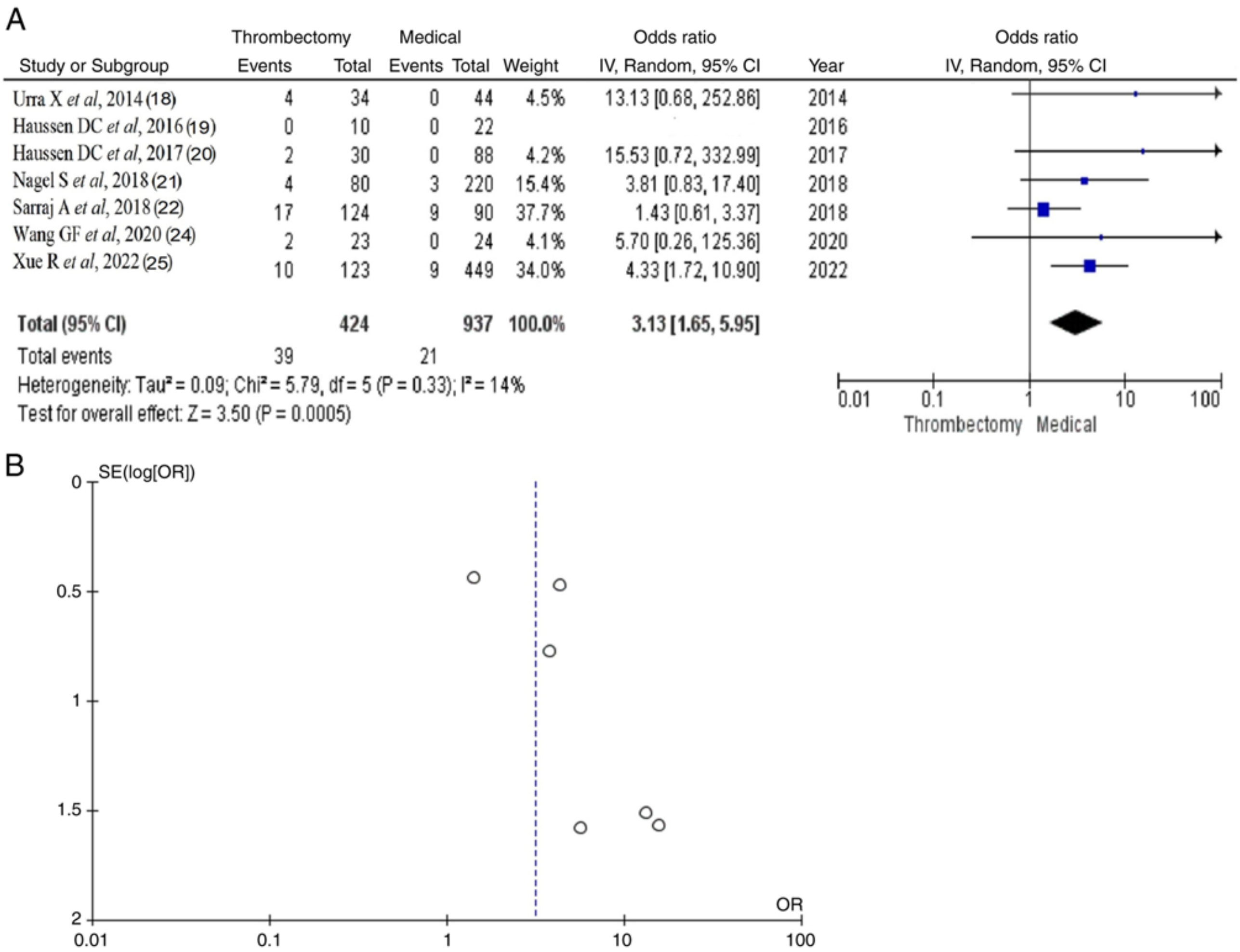

Figure 4. Bleeding ORs. (A) Forest plot of the bleeding ORs demonstrated a statistically significant difference between groups (total OR 3.13, CI 95% 1.65-5.95; P<0.05). (B) Funnel plot of the bleeding ORs demonstrated very low heterogeneity (P=0.33, and I^2=14%). Medical, medical management; OR, odds ratio.

Looking at the funnel plot of the same parameter, it was found that the study results without the 'Wang *et al*, 2020' (24) article displayed an improved dispersion with no publication bias (Fig. 5C and D).

Mortality. Mortality data were available in six of the eight articles (18,19,21,22,24,25): A total of 81/1,243 (6.5%) patients, including 30 out of 394 (7.6%) from the ET group and 51 (6.0%) out of 849 from the medical management group. The statistical analysis demonstrated no statistically significant difference (OR 1.37, CI 95 % 0,55-3.41; P=0.50) but indicated heterogeneity (P=0.10 and I^2=45 %) (Fig. 6A). By testing the sensitivity (Table IV), after removing the article by 'Nagel S *et al*, 2018' (21), it was found a statistically significant difference (OR 1.94, CI 95% 1.02-3.69; P<0.05) with no heterogeneity (P=0.40 and I^2=2%) (Fig. 6B). Looking at the funnel plot of the same parameter, it was found that the study results without the 'Nagel S *et al*, 2018' (21) article displayed an improved dispersion with very little publication bias (Fig. 6C and D).

Discussion

The present study suggested that medical management for LVO strokes with minimal symptoms was associated with fewer complications compared with ET intervention. More precisely, atrial fibrillation was the only statistically significant parameter related to bleeding and mortality in patients with LVO strokes with minimal symptoms. Interestingly, the rates of the mRS score of 0-2 (indicating a good outcome) at discharge and the morbidity (KPS <80) showed no association with medical management or ET therapy in those patients.

The findings of the present meta-analysis pointed out that ET therapy may be associated with a high risk of bleeding and mortality in patients with LVO presenting with mild symptoms (NIHSS score ≤8).

The absence of benefits from ET therapy is consistent with the findings of several previous studies (26-29). However, a multicenter observational study reported that ET therapy was effective in recanalizing the occluded vessel but increased the risk of serious bleeding significantly without improving the functional outcome, suggesting that it was not justified routinely in minor strokes (18). The current study showed that ET therapy is related to a high risk of bleeding and mortality in patients with LVO presenting mild symptoms (NIHSS score ≤8). This may be attributed to several reasons, such as the acceptable collateral condition that developed in patients with LVO and mild symptoms, which predisposes to bleeding and reduces the advantages of ET.

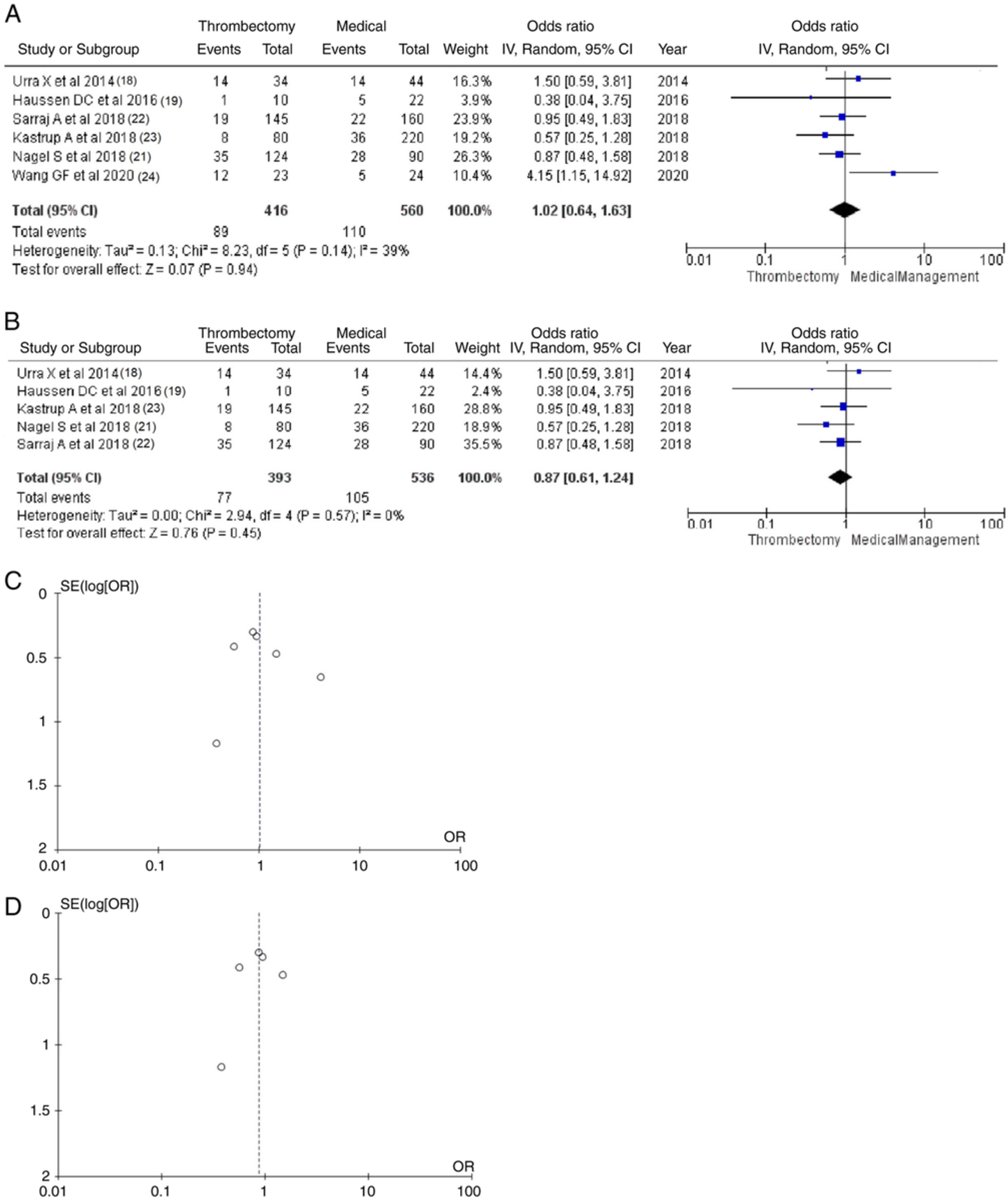

Figure 5. Morbidity ORs. (A) Forest plot of morbidity ORs demonstrated no statistically significant difference between groups (total OR 1.02, CI 95% 0.64-1.63; P=0.94). (B) Forest plot of morbidity ORs obtained by excluding the 'Wang *et al*, 2020' (24) article demonstrated again no statistically significant difference between the groups (total OR 0.87, CI 95% 0.61-1.24; P=0.45). (C) Funnel plot of the morbidity ORs between groups, with the 'Wang *et al* 2020' (24) article and heterogeneity (P=0.14 and I^2=39%). (D) Funnel plot of the morbidity ORs between groups, without the 'Wang *et al* 2020' (24) article and heterogeneity (P=0.57 and I^2=0%). OR, odds ratio.

In addition, the recent meta-analysis showed that ET therapy, compared with medical management alone, is associated with higher rates of bleeding and mortality outcomes in patients with atrial fibrillation. A possible explanation is the higher proportion of atrial fibrillation in the ET group, an extensively reported risk factor for intracerebral haemorrhage (30,31).

In agreement with previous cohorts of patients presenting with mild symptoms, the treatment modality had a high percentage of good early clinical outcomes and an excellent

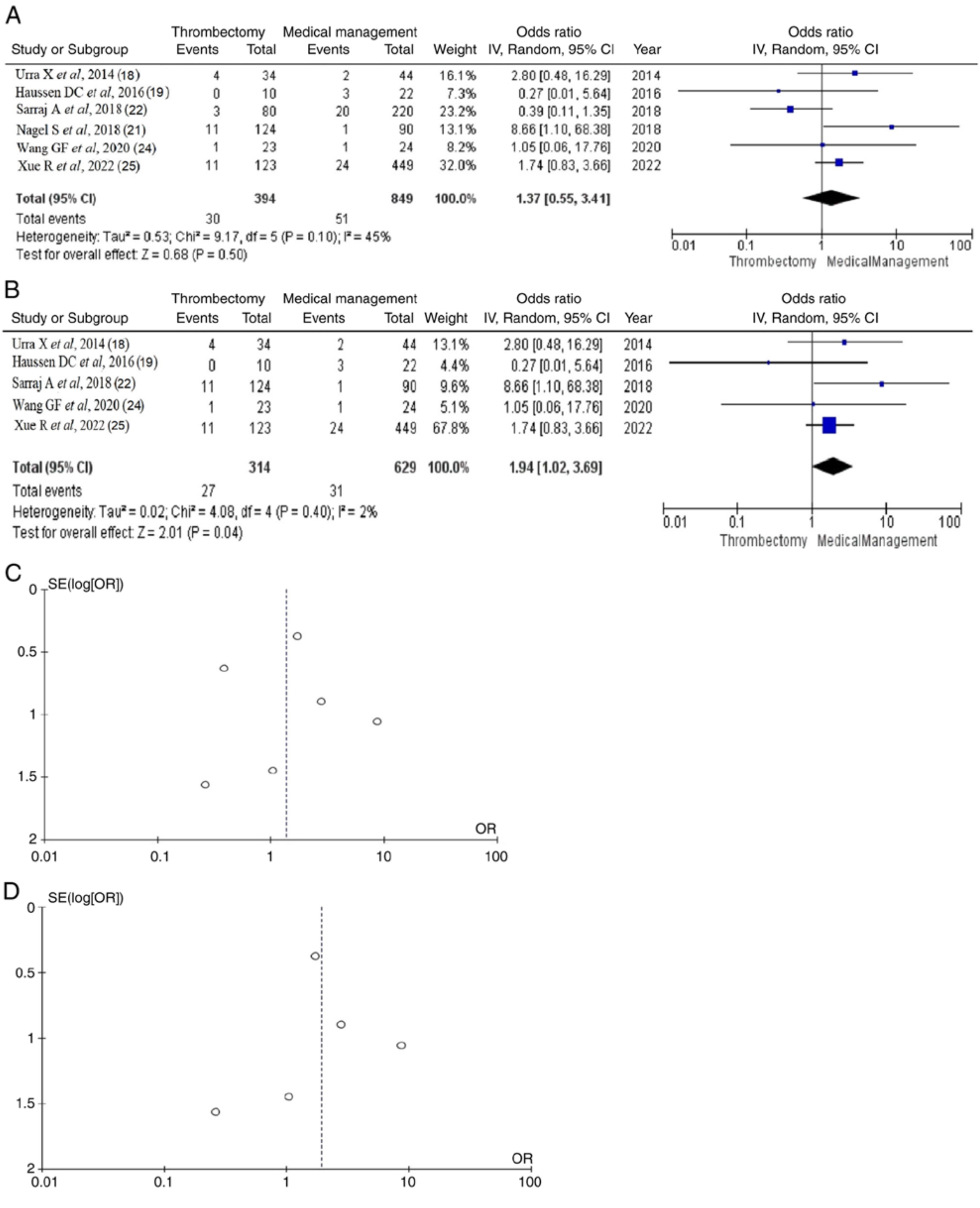

Figure 6. Mortality ORs. (A) Forest plot of mortality ORs demonstrated no statistically significant difference between groups (total OR 1.37, CI 95 % 0.55-3.41; P=0.50). (B) Forest plot of mortality ORs without the 'Nagel *et al*, 2018' (21) article demonstrated a statistically significant difference between the groups (total OR 1.94, CI 95% 1.02-3.69; P<0.05). (C) Funnel plot of the mortality ORs between the groups, with the 'Nagel *et al*, 2018' (21) article and with heterogeneity (P=0.10 and I^2=45%). (D) Funnel plot of the mortality ORs between groups without the 'Nagel *et al*, 2018' (21) article and without heterogeneity (P=0.40 and I^2=2%). ET, endovascular thrombolysis; medical, medical management; OR, odds ratio.

early clinical outcome (23); however, even after excluding patients with contraindications for an ET, the clinical outcome was not significantly different between ET and medical management in patients with an admission NIHSS ≤8. The aforementioned results are similar to the ones shown in the present study, with mRS 0-2 and morbidity having no association with medical management or ET therapy in those patients.

Prior studies reported on outcomes achieved using ET therapy in milder stroke patients but were limited because of a single-center study design (20), a small number of patients (18-20) or the lack of a similar medical management group (32). These uncertain results highlight the need for higher-quality data for this population.

There are several limitations in the present study. First, most of the eligible reports that were included were retrospective. These retrospective studies are affected by low accuracy and data loss. Additionally, the study design differed significantly among the included studies, e.g. the duration of follow-up (e.g., 30-90 days).

In conclusion, the routine use of ET was not significantly favorable for the early clinical or radiological outcome in patients with mild strokes and LVO compared with medical management alone. However, the present results suggested that ET could be beneficial only in patients with NIHSS ≥8. It is also undisputable that a randomized trial is needed to determine the difference in outcome between these two treatment modalities in these patients.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

GF and VEG conceptualized the study. VEG, IT, GF, PP, ISA, DAS and NT analyzed the data and wrote and prepared the draft of the manuscript. VEG and GF provided critical revisions. All authors contributed to the manuscript revision. All authors read and approved the final manuscript. GF and VEG confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article.

References

1. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, Mensah GA, Norrving B, Shiue I, Ng M, *et al*: Global burden of stroke and risk factors in 188 countries, during 1990-2013: A systematic analysis for the global burden of disease study 2013. Lancet Neurol 15: 913-924, 2016.
2. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, *et al*: Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 359: 1317-1329, 2008.
3. IST-3 collaborative group: Effect of thrombolysis with alteplase within 6 h of acute ischaemic stroke on long-term outcomes [the third International Stroke Trial (IST-3)]: 18-month follow-up of a randomised controlled trial. Lancet Neurol 12: 768-776, 2013.
4. Strbian D, Piironen K, Meretoja A, Sairanen T, Putaala J, Tiainen M, Artto V, Rantanen K, Häppölä O, Kaste M, *et al*: Helsinki stroke thrombolysis registry group: Intravenous thrombolysis for acute ischemic stroke patients presenting with mild symptoms. Int J Stroke 8: 293-299, 2013.
5. Köhrmann M, Nowe T, Huttner HB, Engelhorn T, Struffert T, Kollmar R, Saake M, Doerfler A, Schwab S and Schellinger PD: Safety and outcome after thrombolysis in stroke patients with mild symptoms. Cerebrovasc Dis 27: 160-166, 2009.
6. Baumann CR, Baumgartner RW, Gandjour J, von Büdingen HC, Siegel AM and Georgiadis D: Good outcomes in ischemic stroke patients treated with intravenous thrombolysis despite regressing neurological symptoms. Stroke 37: 1332-1333, 2006.
7. Meyers PM, Schumacher HC, Connolly ES Jr, Heyer EJ, Gray WA and Higashida RT: Current status of endovascular stroke treatment. Circulation 123: 2591-2601, 2011.
8. Pierot L, Soize S, Benaissa A and Wakhloo AK: Techniques for endovascular treatment of acute ischemic stroke: From intra-arterial fibrinolytics to stent-retrievers. Stroke 46: 909-914, 2015.
9. Selim MH and Molina CA: Management of acute stroke patients with rapidly resolving deficits and persistent vascular occlusion: A real clinical equipoise. Stroke 41: 3007-3008, 2010.
10. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, Jauch EC, Jovin TG, Yan B, Silver FL, *et al*: Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 368: 893-903, 2013.
11. Cerejo R, Cheng-Ching E, Hui F, Hussain MS, Uchino K, Bullen J and Toth G: Treatment of patients with mild acute ischemic stroke and associated large vessel occlusion. J Clin Neurosci 30: 60-64, 2016.
12. Heldner MR, Zubler C, Mattle HP, Schroth G, Weck A, Mono ML, Gralla J, Jung S, El-Koussy M, Lüdi R, *et al*: National institutes of health stroke scale score and vessel occlusion in 2152 patients with acute ischemic stroke. Stroke 44: 1153-1157, 2013.
13. Mokin M, Masud MW, Dumont TM, Ahmad G, Kass-Hout T, Snyder KV, Hopkins LN, Siddiqui AH and Levy EI: Outcomes in patients with acute ischemic stroke from proximal intracranial vessel occlusion and NIHSS score below 8. J Neurointerv Surg 6: 413-417, 2014.
14. Foster RL: Reporting guidelines: Consort, prisma, and squire. J Spec Pediatr Nurs 17: 1-2, 2012.
15. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M and Tugwell P: The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute, Ottawa, ON, 2014. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
16. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, *et al*: The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 343: d5928, 2011.
17. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Updated March 2011.
18. Urra X, Román LS, Gil F, Millán M, Cánovas D, Roquer J, Cardona P, Ribó M, Martí-Fàbregas J, Abilleira S, *et al*: Medical and endovascular treatment of patients with large vessel occlusion presenting with mild symptoms: An observational multicenter study. Cerebrovasc Dis 38: 418-424, 2014.
19. Haussen DC, Bouslama M, Grossberg JA, Anderson A, Belagage S, Frankel M, Bianchi N, Rebello LC and Nogueira RG: Too good to intervene? Thrombectomy for large vessel occlusion strokes with minimal symptoms: An intention-to-treat analysis. J Neurointerv Surg 9: 917-921, 2017.
20. Haussen DC, Lima FO, Bouslama M, Grossberg JA, Silva GS, Lev MH, Furie K, Koroshetz W, Frankel MR and Nogueira RG: Thrombectomy versus medical management for large vessel occlusion strokes with minimal symptoms: An analysis from STOPStroke and GESTOR cohorts. J Neurointerv Surg 10: 325-329, 2018.
21. Nagel S, Bouslama M, Krause LU, Küpper C, Messer M, Petersen M, Lowens S, Herzberg M, Ringleb PA, Möhlenbruch MA, *et al*: Mechanical thrombectomy in patients with milder strokes and large vessel occlusions. Stroke 49: 2391-2397, 2018.

22. Sarraj A, Hassan A, Savitz SI, Grotta JC, Cai C, Parsha KN, Farrell CM, Imam B, Sitton CW, Reddy ST, *et al*: Endovascular thrombectomy for mild strokes: How low should we go? Stroke 49: 2398-2405, 2018.
23. Kastrup A, Brunner F, Hildebrandt H, Roth C, Winterhalter M, Giessing C and Papanagiotou P: Endovascular therapy versus thrombolysis in patients with mild strokes and large vessel occlusions within the anterior circulation. Interv Neurol 7: 431-438, 2018.
24. Wang GF, Zhao X, Liu SP, Xiao YL and Lu ZN: Efficacy and safety of mechanical thrombectomy for acute mild ischemic stroke with large vessel occlusion. Med Sci Monit 26: e926110, 2020.
25. Xue R, Zhong W, Zhou Y, He Y, Yan S, Chen Z, Wang J, Gong X and Lou M: Endovascular treatment for minor acute ischemic strokes with large vessel occlusion. J Am Heart Assoc 11: e027326, 2022.
26. Volny O, Zerna C, Tomek A, Bar M, Rocek M, Padr R, Cihlar F, Nevsimalova M, Jurak L, Havlicek R, *et al*: Thrombectomy vs medical management in low NIHSS acute anterior circulation stroke. Neurology 95: e3364-e3372, 2020.
27. Goyal N, Tsivgoulis G, Malhotra K, Ishfaq MF, Pandhi A, Frohler MT, Spiotta AM, Anadani M, Psychogios M, Maus V, *et al*: Medical management vs mechanical thrombectomy for mild strokes: An international multicenter study and systematic review and meta-analysis. JAMA Neurol 77: 16-24, 2020.
28. Manno C, Disanto G, Bianco G, Nannoni S, Heldner M, Jung S, Arnold M, Kaesmacher J, Müller M, Thilemann S, *et al*: Outcome of endovascular therapy in stroke with large vessel occlusion and mild symptoms. Neurology 93: e1618-e1626, 2019.
29. Wu X, Khunte M, Payabvash S, Zhu C, Brackett A, Matouk C, Gandhi D, Sanelli P and Malhotra A: Outcomes after thrombectomy for minor stroke: A meta-analysis. World Neurosurg 149: e1140-e1154, 2021.
30. Tian B, Tian X, Shi Z, Peng W, Zhang X, Yang P, Li Z, Zhang X, Lou M, Yin C, *et al*: Clinical and imaging indicators of hemorrhagic transformation in acute ischemic stroke after endovascular thrombectomy. Stroke 53: 1674-1681, 2022.
31. Van Kranendonk KR, Treurniet KM, Boers AMM, Berkhemer OA, van den Berg LA, Chalos V, Lingsma HF, van Zwam WH, van der Lugt A, van Oostenbrugge RJ, *et al*: Clinical and imaging markers associated with hemorrhagic transformation in patients with acute ischemic stroke. Stroke 50: 2037-2043, 2019.
32. Dargazanli C, Consoli A, Gory B, Blanc R, Labreuche J, Preda C, Bourdain F, Decroix JP, Redjem H, Ciccio G, *et al*: Is reperfusion useful in ischaemic stroke patients presenting with a low national institutes of health stroke scale and a proximal large vessel occlusion of the anterior circulation? Cerebrovasc Dis 43: 305-312, 2017.